REMARKS

In the Office Action dated April 15, 2010, claims 1-8, 13 and 16-83 were pending, of which claims 2-4, 6-8, 17-31 and 34-82 were withdrawn from consideration. Claims 1, 5, 13, 16, 32-33 and 83 were under examination and were rejected. Specifically, claims 16, 32, 33, and 83 were objected to because they recite non-elected subject matter in the alternative. Claims 1, 5, 13, 16, 32-33 and 83 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Markowitz (US 2004/0038220). Claims 1, 5, 13, 16, 32-33 and 83 were also rejected under 35 U.S.C. §102(a) and §102(b) as allegedly anticipated by WO 01/49879, Ørntoft et al. Additionally, claims 1, 5, 13, 16, 32, 33, and 83 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with both the enablement requirement and the written description requirement. The Examiner has, however, indicated the allowable claim language:

> "A method for determining an increased likelihood of the presence of colorectal adenoma in a human, said method comprising
>
> measuring the level of an mRNA which comprises the RNA equivalent of SEQ ID NO: 7 in a gastrointestinal tract sample from said human and
>
> determining an increased likelihood of the presence of colorectal adenoma when the level of said mRNA is increased in said human relative to the normal level of said mRNA in gastrointestinal tract samples from healthy individuals."

This Response addresses each of the Examiner's rejections and objections. Favorable consideration of the presently presented claims is therefore respectfully requested.

Claim Amendments

Claim 1 has been amended to further delineate the method as based on "measuring the level of an mRNA or the protein encoded by said mRNA, ... wherein said mRNA comprises the RNA equivalent of SEQ ID NO: 7." Independent claim 16 has been similarly amended. Claim 5

has been canceled. Claim 13 has been amended to conform to the present language in claim 1.

These amendments are consistent with the Examiner's suggestion of allowable subject matter. Support for detection based on measuring the level of protein is found in the specification, e.g., page 23, lines 16-30. Further, the language, "the RNA equivalent of SEQ ID NO: 7", would be clear to those skilled in the art. SEQ ID NO: 7 sets forth a DNA sequence as part of a gene which has been named KIAA1199. The portion of the RNA molecule transcribed from this gene, which portion corresponds to SEQ ID NO: 7, would be understood to mean the RNA equivalent of SEQ ID NO: 7.

No new matter is introduced by the foregoing amendments. Upon entry of the amendments, claims 1-4, 6-8, 13 and 16-83 will be pending, and claims 1, 13, 16, 32-33 and 83 will be under examination

Claim Objection

Claims 16, 32, 33, and 83 were objected to because they recite non-elected subject matter in the alternative.

Applicants note that rejoinder of the additional combinations which require SEQ ID NO: 7 will be considered once the claims based on elected SEQ ID NO: 7 are found allowable. Therefore, Applicants wish to maintain the recitation of the additional combinations because, as discussed hereinbelow, the subject matter based on elected SEQ ID NO: 7 is patentable.

35 U.S.C. § 102 Rejections

Claims 1, 5, 13, 16, 32-33 and 83 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Markowitz (US 2004/0038220). These claims are also rejected under 35 U.S.C.

§102(a) and §102(b) as allegedly anticipated by WO 01/49879, Ørntoft et al.

Both rejections are raised based on the Examiner's determination that instant SEQ ID NO: 7 is not disclosed in the priority document, U.S. Provisional Application 60/322,288.

However, instant SEQ ID NO: 7 was disclosed in the provisional application as SEQ ID NO: 77. At the time of converting the provisional application to a PCT application, the sequences were renumbered. Accordingly, the cited references do not qualify as prior art relative to the claimed invention. Withdrawal of the rejections under 35 U.S.C. §102 is respectfully requested.

35 U.S.C. § 112, First Paragraph Rejections

Claims 1, 5, 13, 16, 32, 33, and 83 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement and written description requirements.

Applicants believe that most of the issues underlying the rejections, which are raised by the Examiner, are moot in light of the instant amendments to the claims. Specifically, Applicants have amended the claims in line with the Examiner's suggestion to detect, e.g., the level of the mRNA which comprises the RNA equivalent of SEQ ID NO: 7. See claims 1 and 16.

Applicants have, however, included measuring the level of "the protein encoded by said mRNA", and also have maintained the reference to "a blood, serum, stool or gastrointestinal tract sample". As submitted below, Applicants maintain that these aspects of the claimed method are fully supported by the specification.

Regarding the aspect of the claimed method based on detection of proteins, the Examiner states in the Office Action that the specification only shows differential expression in relation to mRNA transcripts but not in relation to protein. The Examiner ultimately concludes that since SEQ ID NO: 7 occurs in an intron region of KIAA1199, the mRNA which was detected

does not code for an actual protein product.

Applicants respectfully disagree.

In the first instance, referring to paragraph 7 of the Pedersen Declaration, the Examiner seems to suggest that SEQ ID NO: 7 would not appear in any mRNA transcript, because SEQ ID NO: 7 allegedly occurs in an intron region. Quite to the contrary, the Declaration discussed the existence of transcripts transcribed from regions which had been annotated as intronic sequences ("so-called 'intronic sequences'"), suggesting that the annotation was not entirely accurate. Further, SEQ ID NO: 7 was initially identified based on differential expression, as disclosed in the specification, dictating that SEQ ID NO: 7 must appear in the mRNA transcript(s).

mRNA is generally synthesized for the purpose of subsequent translation to a protein. Accordingly, screening for the KIAA1199 protein is a logical extrapolation of the mRNA data which appear in the specification. It is the Examiner's assertion which would describe a far more rare situation, that is the generation of an mRNA which does not translate to a protein.

In this connection, the Examiner's attention is also directed to the data provided in Exhibit 4 of the Pedersen Declaration (previously submitted), which demonstrate that increased levels of the translation product of a SEQ ID NO: 7-containing gene was detectable in stool samples of patients with colorectal adenoma.

Regarding the sample source, Applicants respectfully submit that the notion that detection of a biomarker in tissue samples translates to detectable changes in blood or serum levels is well documented and amply supported by the art, and confirmation thereof would not require undue experimentation.

In support of Applicants' position in this regard, Applicants respectfully direct the Examiner's attention to the data in the Pedersen Declaration, showing the upregulation in the level

of expression of KIAA1199 in stool and plasma samples. Specifically, the results show that increased levels of KIAA1199 protein in stool samples were detected an indirect ELISA using a monoclonal antibody directed to KIAA1199 protein. Dr. Pedersen stated in the Declaration that increased levels of mRNA of KIAA1199 are believed to have also occurred in the same stool samples. Additionally, the results also show that approximately 30% of adenoma patients exhibited a significant increase in KIAA1199 mRNA in the plasma, while only one out of ten normal patients showed an increase in KIAA1199 mRNA in the plasma.

Although actual analysis of stool and plasma samples is not specifically exemplified in the specification, based on the disclosure of colonoscopy samples provided in the present application, the teachings in the art and the common general knowledge of the skilled person, one would have reasonably expected that gene expression which is altered in colorectal neoplasms would also be detectable in stools and in blood samples. Applicants again direct the Examiner's attention to the Pedersen Declaration. As Dr. Pedersen explained (paragraph 13), it is well known that all solid tumors are associated with a certain level of apoptosis. Neoplastic cells that are apoptosed are then shed into the stools, where they are detectable. Further, where shedding of cells into stools occurs, there generally also exists apoptotic leakage into the blood.

In light of the data showing elevated levels of expression of KIAA1199 in stool samples, and the fact that colorectal neoplasms which shed cells into the stool are often also associated with leakage into the blood, Applicants respectfully submit tissue biopsies, stool and peripheral blood are all appropriate biological samples for analysis for practicing the claimed invention. As stated in the Pedersen Declaration (paragraph 14), once an upregulated expression of a biomarker is established based on tissue biopsy sample, the experimentation involved in confirming that elevated expression can also be detected in stool and blood samples would be

routine and not excessive.

The Examiner asserts at the bottom of page 14 of the Action, that Figure 1 in Exhibit III of the Declaration only shows increases in KIAA1199 gene expression in colorectal neoplasias and non-colorectal adenomas. This is incorrect. The figure legend clearly indicates that the results which are shown are the analysis of results of colon tissue specimens from 30 normal, 21 adenoma, and 21 cancer patients.

At page 16 of the Office Action, the Examiner is again stating that she will not accept the argument that one would expect to find KIAA1199 mRNA and protein in the blood. The Examiner argues that it is not predictable which markers would be detectable in the blood and which markers would not. Applicants request that the Examiner reconsider in light of the actual evidence that these markers are found in the blood, as presented in the Delcaration.

The Examiner also states that although the Declaration does show that KIAA1199 protein is upregulated in stool and serum, this is insufficient and does not provide a nexus with the fact that the SEQ ID NO:7 mRNA which was found to be upregulated is responsible for encoding this protein.

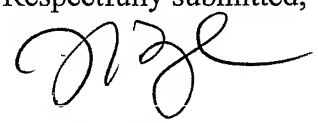
As discussed above, the Examiner seems to have misunderstood the Declaration, leading to an incorrect conclusion that SEQ ID NO: 7 would not appear in mRNAs. SEQ ID NO: 7 does appear in mRNA transcript, as supported by the expression data in the specification and the data presented in the Declaration.

In view of the foregoing, it is respectfully submitted that the present claimed method is fully supported by the specification in full compliance with 35 U.S.C. §112, first paragraph. Withdrawal of the enablement and written description rejections is therefore respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited

Respectfully submitted,



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